REMARKS

The above amendments have been provided based on the format described at 1265 Off. Gaz. Pat. Office 87 (December 17, 2002) and as authorized by Deputy Commissioner for Patents, Stephen Kunin on January 31, 2003.

Claims 1 and 5-23 were pending. The Examiner withdrew 8-18 from consideration following a restriction requirement. Claims 8-18 are cancelled herewith. Claims 1, 5-7, and 19-23 were rejected in the previous Office action, and no claims were allowed. Claims 1, 5-7, and 19-23 are presently pending.

Formal Matters

Applicants gratefully acknowledge the acceptance of the amended title.

The Office has requested that the new abstract be presented on a separate page. Applicants have submitted the new abstract on a separate page.

Applicants have amended the specification to update the status of related applications.

The Office asserts that a Terminal Disclaimer has not been submitted in the instant application. The Terminal Disclaimer was hand delivered to the Examiner on November 19, 2002. A copy of the postcard certifying delivery and the Terminal Disclaimer are included herewith as Exhibits A and B, respectively, for the convenience of the Examiner.

Applicants gratefully acknowledge the acceptance of the substitute declaration.

The Office stated that a complete reply to the final rejection must include the cancellation of claims 8-18. Please cancel claims 8-18 without prejudice.

Applicants gratefully acknowledge that claims 1, 5-7, and 19-23 are in compliance with the requirements under 35 U.S.C. 103 (a).

The Examiner has stated that references not considered with the IDS forms received March 14, 2000 and September 10, 2001 because the references were not in Examiner's file. Applicants note that all references from the IDS were provided to the Examiner by hand delivery on November 19, 2002. Applicants have included the return postcard signed by Examiner Gitomer indicating the receipt of these references as Exhibit A for the Examiner's reference. Furthermore, Applicants note that Examiner Gitomer indicated to Dr. Wityshyn that such hand delivery would insure the receipt and consideration of the submitted references. **Applicants respectfully request specific instructions from the Examiner as to how to deliver the references to him so that he may retain copies to examine.**

Applicants again respectfully submit that

> a copy of any patent, publication, pending U.S. application, or other information listed in an information disclosure statement is not required to be provided if: (1) the information was previously cited by or submitted to, the Office in a prior application, provided that the prior application is properly identified in the IDS and is relied on for an earlier date under 35 U.S.C. § 120 ...

Manual of Patent Examination Procedure § 609 III(A)(2) (8th ed. 2001). Applicants have previously submitted all of the references in the instant application in related applications, and thus are in full compliance with the IDS requirements under § 609 of the *Manual of Patent Examination Procedure*. Nonetheless, Applicants have again enclosed herewith courtesy copies of these references in an effort to expedite prosecution.

Applicants again respectfully remind the Examiner of the mandate regarding a speedy prosecution by the Patent & Trademark Office. According to the *Manual of Patent Examination Procedure*, "the invention as disclosed and claimed should be thoroughly searched in the first action and the references fully applied" to "bring the prosecution to as speedy conclusion as possible and at the same time to deal justly by both the applicant and the public." *Manual of Patent Examination Procedure* § 706.07. "[I]t is to the interest of the applicants as a class as well as to that of the public that prosecution of an application be confined to as few actions as is

consistent with a thorough consideration of its merits." *Id.* Furthermore, Applicants note that the failure to examine the references properly submitted in the IDS of properly identified related applications requires that the Examiner remove the finality of the rejection mailed March 6, 2003 if the Examiner introduces a new ground of rejection based on the properly submitted references. *Manual of Patent Examination Procedure* § 706.07(a).

In light of the above, Applicants respectfully submit that the objection to the specification has been overcome. Therefore, Applicants request the withdrawal of the objections.

Obviousness-Type Double Patenting Rejection

Claims 1, 5-7, and 19-23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-6 of copending Application No. 09/113,947, now allowed as 6,462,019. Applicants traverse this rejection.

Applicants submitted a terminal disclaimer over claims 1-6 of U.S. Patent No. 6,462,019 on November 19, 2002 via hand delivery. This is included herein as Exhibit B. Therefore, Applicants note that the maintenance of this rejection is without grounds and request the withdrawal of the rejection.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 5 and 22 are rejected under 35 U.S.C. § 112, first paragraph as lacking written description of treating any of the disorders in any vertebrates including humans. According to the Office, the specification as originally filed provides no written description of treating any of the disorders in any vertebrate including humans. Claims 1, 5-7, 19, and 22-23 are rejected under 35 U.S.C. § 112, first paragraph because the specification is not enabling for a peptidyl aldehyde. The Office asserts that undue experimentation would be required to determine which such aldehyde would work in the instant invention. The Office also alleges that the term "a peptidyl aldehyde" reads on an infinite number of compounds, and most are unlikely to work in

the claimed invention. According to the Office, there is no guidance or direction presented to direct one to determine which aldehydes would work in the broadly claimed invention. The Office also dismisses Dr. Mundy's declaration as providing enablement for the claimed methods. Applicants respectfully traverse these rejections for reasons of record and those included below.

1. The specification provides adequate written description for the treatment of vertebrates using the claimed methods.

Contrary to the assertion by the Office, the specification as filed provided detailed written description for the treatment of the disorders in vertebrates, including humans. The specification discloses treatment within the context of the claimed methods at page 10, lines 1-8. Detailed disclosure regarding the mode of administration and the formulation of peptidyl aldehydes for use in the claimed methods are found in the specification at page 11, line 9 to page 15, line 23. The specification provides guidance as to the dosage of the compound for use in the claimed methods at page 17, line 21 to page 18, line 3. The specification discloses the outcome of the claimed treatment at page 16, line 26 to page 17, line 20. Moreover, the specification specifically discloses vertebrates as the recipients of the claimed treatment at page 9, lines 23-24, and provides guidance for and working examples of treating vertebrates in the specification at page 22, line 22 to page 25, line 24 and Examples 3 and 7. Applicants respectfully submit that mice are vertebrates. As the specification discloses the treatment of mice using peptidyl aldehydes to promote bone growth, the assertion by the Office that the specification has "no written description of treating any of the disorders in any vertebrates" is without merit.

The specification conveys with reasonable clarity to a skilled person in the art that Applicants had possession of the claimed methods at the time of filing, thus meeting the requirement under 35 U.S.C. § 112, first paragraph. Applicants disclose working examples in the form of *in vitro* or *in vivo* vertebrate models (*i.e.*, murine) recognized by the skilled artisan. Furthermore, Applicants disclose how to make and use the claimed methods as evidenced by the detailed disclosure of modes of administration, formulations of compounds, identity of compounds, dosages, recipients of treatment, and the desired outcome of the treatment.

However, the novelty of the claimed methods does not lie in the form of treatment, but rather in the use of compounds with a particular biological activity, peptidyl aldehydes that inhibit proteasomal activity, to stimulate bone growth. The identity of these compounds and the methods to identify such compounds are disclosed in the specification and are supported by working examples using vertebrates. Therefore, the critical features of the claimed methods are disclosed, meeting the written description requirement under 35 U.S.C. § 112, first paragraph.

2. The specification is enabling for a peptidyl aldehyde that is a proteasomal inhibitor.

Contrary to the position taken by the Examiner that the claims are drawn to "a peptidyl aldehyde", the claims are drawn to "a peptidyl aldehyde **that is a proteasomal inhibitor**."

Applicants respectfully submit that if a compound must retain a certain biological activity to be within the scope of the claimed invention, and one of skill in the art is clearly enabled to perform assays to determine such biological activity using routine experimentation disclosed in the specification, the disclosure is fully enabling. *Ex Parte Mark,* 12 U.S.P.Q.2d 1904 (Bd. Pat. App. & Int. 1989) (holding that method claims to produce biologically active muteins by modifying biologically-nonessential cysteines was fully enabled because any mutein within the scope of the claims must have retained its biological activity and the experimentation required to determine biological activity for any given mutein was routine for one of ordinary skill in the art). *See* Exhibit C. The peptidyl aldehyde of the claimed methods is one that is a proteasomal inhibitor. Proteasomal inhibition is a certain biological activity that a peptidyl aldehyde must possess to be within the scope of the claimed methods. Therefore, the peptidyl aldehyde of the claimed methods falls squarely within the holding of *Ex Parte Mark*, binding precedent on the Office.

a. The specification provides guidance and direction to determine which peptidyl aldehydes will work in the claimed methods.

The specification discloses multiple peptidyl aldehydes that are proteasomal inhibitors as compounds that are useful in the claimed methods. For example, PSI, MG-132, MG-115, MG-

101, and ALLN are all peptidyl aldehydes and are disclosed on page 29 of the specification. The specification provides adequate guidance in the assessment of proteasomal inhibitory activity of the compounds and clearly indicates that this biological activity defines the group of peptidyl aldehydes useful in the claimed methods. *See, e.g.*, the specification at pate 18, lines 10-23, and Examples 4 and 5. The specification also discloses the use of multiple peptidyl aldehydes in *in vitro* and *in vivo* assays for bone growth. For example, peptidyl aldehydes are employed in the working examples of Example 2 (PSI, MG-132, MG-115), Example 3 (PSI, MG-132), Example 4 (PSI, MG-132, MG-115), Example 5 (PSI, MG-132), and Example 6 (PSI). As previously discussed in the prior response received November 19, 2002, these assays are both conventional and well known in the art, and therefore the performance of these assays is merely routine experimentation.

b. The specification enables the full scope of the claims.

The sufficiency of the disclosure in the specification is supported by the declarations of Dr. Mundy and Dr. Garrett submitted pursuant to 37 C.F.R. § 1.132. The Declaration of Dr. Mundy, submitted by hand delivery on November 19, 2002, provides additional evidence that peptidyl aldehydes that are proteasomal inhibitors stimulate bone growth. The Declaration of Dr. Garrett, attached as Exhibit D, provides further evidence that the genus of peptidyl aldehydes that are proteasomal inhibitors are enabled by the specification. Specifically, Dr. Garrett's declaration employs four different peptidyl aldehydes that are proteasomal inhibitors - PSI, MG-132, MG-115, and ALLN. In Table 1, for example, using the guidance found in the specification at page 20, line 11 to page 21, line 11 and in Example 2, PSI, MG-132, MG-115, and ALLN are shown to inhibit proteasomal activity and stimulate bone formation. The data demonstrate that the induction of bone formation correlates with the induction of BMP-2 protein, a correlation that is disclosed throughout the specification. *See, e.g.*, Example 1. Tables 3 and 4 show additional results confirming the proteasomal inhibitory activity and the bone formation activity of PSI, MG-132, and MG-115 as disclosed in the specification. Thus, both the specification and

the supporting declaration disclose multiple operative embodiments of compounds useful in the claimed methods.

Applicants note that

> [f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art ... would expect the claimed genus to be used in that manner without undue experimentation.

Manual of Patent Examination Procedure § 2164.03 (emphasis added).

A skilled artisan can determine which embodiments were conceived, but not yet made, that are operative in the claimed methods with an expenditure of no more effort than is normally required in the art using the guidance and working examples in the specification. All that is required for the practice of the instant method is the determination that a peptidyl aldehyde is a proteasomal inhibitor using conventional and well known methods as exemplified in the specification. The Office continues to assert that a large number of inoperative embodiments are claimed. However, the Office has not provided scientific reasoning or evidence as to why the specification and supporting declarations are insufficient nor has the Office provided specific technical reasons identifying what information is missing or why one skilled in the art could not supply the information without undue experimentation. Such reasoning and/or evidence is required from the Office. *See Manual of Patent Examination Procedure* § 2164.04.

c. Undue experimentation is not required to practice the claimed methods.

Identifying the peptidyl aldehydes that are proteasomal inhibitors require only routine experimentation. The law allows for routine experimentation in the practice of claimed methods. For example, in *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988), the Court of Appeals for the Federal Circuit found that a claim reciting the use of any high affinity IgM was fully enabled despite the fact that the claim read on the use of nearly an infinite number of particular antibodies. While it would require an enormous amount of effort to practice every embodiment, only a minimal amount was required to practice any one embodiment. In other words, if the

experimentation required is only the use of well known and conventional methods, the experimentation is not undue simply because some experimentation is required. Applicants respectfully submit that the experimentation to identify peptidyl aldehydes that inhibit proteasomal activity is the exactly the type of routine experimentation accepted by the *In re Wands* court.

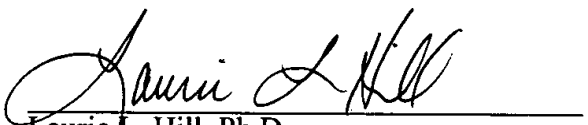
In light of the above, Applicants respectfully submit that the rejections under 35 U.S.C. § 112, first paragraph have been overcome. Therefore, Applicants request the withdrawal of the rejections.

CONCLUSION

Applicants submit that the objections and rejections under 35 U.S.C. § 112 and the judicially-created doctrine of obviousness-type double patenting have been overcome by the above remarks. Early allowance of pending claims 1, 5-7, and 19-23 is respectfully requested. In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 432722002621.

Respectfully submitted,

Dated: May 5, 2003

By: 

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